AGE AS A MODIFYING FACTOR IN THE ASSOCIATION BETWEEN LUNG CANCER IN NON-SMOKING WOMEN AND THEIR HUSBANDS SMOKING STATUS

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ABSTRACT:

A previous analysis (1) of (2) is reviewed and extended. Age is shown to be an important modifying factor in the association between lung cancer in nonsmoking women and their husbands' smoking status. Heterogeneity of the cell specific risk ratios is demonstrated using the Mantel-Haenszel extended test for trend, when the data are stratified by the wife's age. The lack of fit of the multiplicative model contra-indicates the use of a Mantel-Haenszel summary statistic. It is likely that age at entry is confounded with calendar period increases in lung cancer mortality in nonsmoking women.

INTRODUCTION

Hirayama reports (2) on a longitudinal record linkage study of married women who, in 1965, were reported to be nonsmokers. Deaths in the period 1966 to 1981 were linked to a questionnaire given in 1965. In this manner, the cause of death in those women who had died by 1981 was linked to the initial interview in 1965 of both husband and wife to produce the results reported (2). His paper presents the mortality experience of nonsmoking wives by selected causes of death cross-classified by husband's smoking status, husband's drinking status, husband's occupation, green and yellow vegetables daily and husband's age. Here, we restrict our attention to Tables 1 & 2 of (2) in order to focus on the effect of standardising by husband's age rather than by the wife's age when studying the association between these women's lung cancer deaths and their husbands' smoking status.

An earlier paper (1), based on a standard Poisson regression and using the conventional 5% level of significance, indicates, on the basis of these published tables, that

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- husband's smoking is marginally associated with wife's lung cancer mortality, the size of the effect being of borderline statistical significance and dependent on the presence or absence of other factors in the model and the classification of the husband's smoking at entry.
- that husband's drinking habit shows no significant association with his wife's lung cancer mortality.
- that daily intake of green/yellow vegetables shows no significant association with lung cancer mortality.

In contrast, it is concluded in (2) that there is 'a significantly increased risk of' lung cancer mortality 'in relation to the extent of the husband's smoking... The association was significant when observed by age of husbands .. and also by age of wives.'

Tables 1 and 2 of (2) give different tabulations of the 16 years lung cancer mortality in these nonsmoking wives. Table 1 gives the lung cancer death rates by five levels of husband's smoking at entry (Non, Ex, 1-14/d, 15-19/d, 20+/d). Table 2 collapses this to Non, Ex. or 1-19/day, 20+/day, here called Non, Light and Heavy ETS exposure. Table 1 further stratifies the wives' lung cancer death rates by the husband's age at entry whereas Table 2 stratifies by the wife's age at entry. (Since it is the usual practice to adjust for the subject's age rather than her husband's, it is remarkable that this is the only occasion in which Dr Hirayama has adjusted wife's mortality by her own age rather than that of her husband's).

Exhibit 1 summarizes a 'power' model analysis of Tables 1 and 2. The power transform finds the best model within a family of loglinear models which include the multiplicative and additive models. Exhibit 1 shows the residual deviance after fitting the factors for age and ETS exposure to Tables 1 and 2 of (2). Table 1 shows little discrimination among models, all giving good fits. Table 2, in contrast, shows that the additive model fits better than the multiplicative model. Indeed, the best fitting power model has a power of $\rho = 1.14$ which is *beyond* the additive for which $\rho = 1.0$. (The multiplicative model in turn corresponds to a $\rho = 0$). However, all models of Table 1 are better fitting than the best fitting model for Table 2, suggesting that further stratification in five year groups may be necessary to adjust for age or that other covariates may be important.

Exhibit 1

Deviances (df) for additive, multiplicative and best fitting power models

	MODEL		
TABLE	ADDITIVE	POWER	MULTIPLICATIVE
Table 1	3.79 (12)	2.76 (12)	3.24 (12)
Table 2	7.91 (6)	7.85 (6)	10.72 (6)

Model is 1+ Husband's Age(4)+ ETS(5) for Table 1

..... 1+ Wife's Age(4)+ ETS(3) for Table 2

Outcome analyzed is cumulative Lung Cancer Death Rate (1966-1981)

The additive model provided a superior fit when wife's age is used to stratify as in Table 2. This means that risk ratios for ETS exposure change with age at entry. The additive model assumes that a constant excess risk is added to the age dependent death rate from lung cancer. Thus, the substitution of husband's age for wife's age changes the underlying model from the multiplicative to the additive and the appropriate summary statistic from a risk ratio to an excess risk.

The analysis given by (1) of (2) was that recommended by Breslow & Day (3) for cohort studies. Dr Hirayama, however, presents his results in terms of the older and more limited Mantel-Haenszel statistics. Here, we follow (2) in presenting a 'classical' analysis of his results in order to show what Dr Hirayama *might* have reported with the techniques available to him at that time, if the data had been stratified by the subject's age at entry rather than by spousal age.

RESULTS

Hirayama's analysis treats Table 2 as a 2x4x3 contingency table where wives are classified as either having died from lung cancer or not, and are

then further tabulated in 4 ten year age groups by wife's age in 1965 and by 3 levels of husband's cigarette smoking (as reported in 1965).

He analyzes Table 2 by comparing the base line exposure in each age group, Non with Light and Non with Heavy ETS exposures. In other words, Hirayama treats Table 2 as though it were two 2x2x4 tables.

He then presents point estimates of the summary risk ratio for Table 2, and tests for the significance of the weighted risk ratio but omits tests for the homogeneity of the age-specific risk ratios which form his Mantel-Haenszel estimate. (A significant test of homogeneity indicates that the use of the weighted estimate is contra-indicated in that the age-specific risk ratios differ significantly).

Here, we collapse the five ETS levels in Table 1 to Non, Light and Heavy in order to have a similar configuration to Table 2. Now the only difference between (collapsed) Table 1 and Table 2 is the use of husband's age in Table 1 and the the use of wife's age in Table 2.

Exhibit 2

Table 1 Lung Cancer Risk Ratio (1966–1981)

HUSBAND'S SMOKING

		Non vs Light	Non vs Heavy	Non vs Exposed
HUSBAND'S AGE AT ENTRY	40–49	1.55	2.32	1.87
	50–59	1.54	1.90	1.68
	60–69	1.53	1.96	1.64
	70+79	0.71	0.67	0.70
χ^2_{trend}	df=1	0.34	5.6	0.71
$\chi^2_{common\ \psi}$	df=3	1.39	1.13	2.03
$\chi^2_{\psi_{MH}=1}$	df=1	3.16	8.53	5.70
ψ_{MH}		1.43	1.90	1.57

Using the classical Mantel-Haenszel methodology for stratified data, the results of the power modelling on Table 1 were confirmed. Thus, see Exhibit 2, stratification by husband's age and the three levels of ETS exposure (Non, Ex. or 1-19/day , 20+/day, called Non, Light and Heavy here, yielded risk ratios that were reasonably constant across age strata. Testing the

homogeneity of the age-specific risk ratios across the four age strata yielded a homogeneity chi-square on 3 degrees of freedom (χ^2_3) that is not significant at either level of the ETS exposure or at both levels combined (Non vs Exposed).

The test of homogeneity in common use is not powerful (4), especially when applied in this manner to cohort data. A more complete treatment of the test for heterogeneity, as applied to cohort studies, is given in (3). Note, however, that we restrict ourselves to the case-control version of the Mantel-Haenszel approach in order to mirror Dr Hirayama's form of analysis.

A test for trend in the risk ratio over age, based on 1 degree of freedom, is provided here for comparability with the analysis which follows. Exhibit 2 shows that the trend test is not significant, with the possible exception of Non vs Heavy (but the value 5.6 is unstable and may be discounted).

Exhibit 3

Table 2 Lung Cancer Risk Ratio (1966–1981)

HUSBAND'S SMOKING

		Non vs Light	Non vs Heavy	Non vs Exposed
	40–49	2.38	3.30	2.76
WIFE'S	50–59	1.60	1.92	1.72
AGE AT	60–69	1.15	1.02	1.12
ENTRY	70–79	0.09	0.48	0.19
χ^2_{trend}	df=1	4.34	5.48	7.64
$\chi^2_{common\ \psi}$	df=3	11.94	5.41	11.24
$\chi^2_{\psi_{MH}=1}$	df=1	2.28	5.15	3.88
ψ_{MH}		1.36	1.66	1.45

In contrast to the above analysis, a strong statistical interaction between age and ETS exposure (Exhibit 3) is evident when the data are stratified by wife's age. The chi square test for homogeneity is statistically significant ($P < .05$) when comparing Non to Exposed across age, as is the comparison between Non and Light ($P < .01$). The comparison between Non and Heavy ETS exposure (20+/day) is not statistically significant. The Mantel-Haenszel extension test to evaluate trends across *age* for each level of the

husband's smoking status is statistically significant ($P < .05$) at all exposure levels. This indicates a true decrease in the risk ratios with increasing wife's age. Indeed, the statistical significance or P value of the trend over wife's age is of the same order as the trend for a " dose response" relationship between the lung cancer death rate and the husband's smoking status.

These results compare favorably with the results from the more general power analysis. This underscores the need, when doing the classical Mantel-Haenszel analysis, to *first* test the assumption of a common risk ratio before proceeding to use the Mantel-Haenszel summary estimate. If the assumption of a common risk ratio is untenable, it is wrong to proceed to calculate and test the significance of a global estimate. "In this situation, it is more important to try to understand and describe the sources of variation in the relative risk than simply to provide a summary measure" (4, p.138)

Our conclusion, presented at Tokyo, was that the multiplicative model which is implicit in the use of the risk ratio is contra-indicated. The relationship between ETS exposure and lung cancer mortality was demonstrated in these data as best described by the additive model. This leads to 'excess risk' as the appropriate summary statistic.

The lack of fit of the multiplicative model may be seen directly from an examination of the risk ratios by age group. Under the multiplicative model, the risk ratio is assumed to be constant over age, apart from random sampling error. Exhibit 3 shows that the risk ratio falls dramatically with age for Non vs Light, Non vs Heavy and Non vs Exposed. It is unexpected to find such a radical shift in the underlying model, given the stated equivalence in the age structures of husband and wife.

DISCUSSION

The Mantel-Haenszel analysis used in (2) implicitly assumes a multiplicative model. This, in turn, is based on the assumption that the risk ratio for ETS exposure and lung cancer mortality in nonsmoking wives is relatively constant over a 40 year age range in the cohort and over the 16 years of follow-up. This assumption could have been tested in (2) on Table 2 with the techniques available at that time. Here, in our analyses, both the Mantel-Haenszel tests for trend and the commonly used test of homogeneity over strata (4), show a clear indication that the multiplicative model does not hold when the wife's age is used to stratify her cumulative lung cancer mortality covering 16 years.

Age at entry effects encompass both chronological age and cohort differences. In the light of the current finding that the risk ratio falls with age at entry, it is also likely that risk ratios would be found to fall with calendar time.

If tests for a common risk ratio by wife's age at entry had not been statistically significant, then Dr Hirayama's substitution of husband's age for wife's age would have had few implications. But since this switch has been shown to change the underlying statistical model and summary statistic, it is clear that husband's age cannot be use as a proxy for wife's age. There is indeed no good reason to do so as wife's age was recorded along with husband's age at entry to the study in 1965. Since Table 2 is the only occasion on which the wife's age is given, we cannot investigate possible interactions of wife's age with other covariates used by Dr Hirayama in this study. Other causes of death in women are also stratified by husband's age. Thus, we are unable to verify whether the current anomaly exists for other causes of death. It is therefore unknown whether husband's age is a satisfactory surrogate for wife's age in any of those papers by Hirayama which deal with female mortality.

Lung cancer mortality in these nonsmoking wives has been shown to be low compared with the Japanese population (1). This may be true of all female mortality results from this study.

It has been pointed out (1) that stratification by age into 4 ten year age groups may result in substantial residual confounding. Whether stratification was based on husband's or wife's age is irrelevant, since, when "the stratification is too coarse, ... some confounding may remain" (4, p.99). How much of the interaction identified in Exhibit 3 using wife's age might be attributable to an inadequate control of age is unknown. Further, as a consequence of the poor fit of the multiplicative model in that analysis,age and calendar time interaction cannot be ruled out as contributing to a potentially spurious association between lung cancer mortality and ETS. We affirm Breslow & Day's suggestion (3) that five year age groups be used and, that "for a long study, it is appropriate to partition the time axis into several intervals" (4, p.201). A true cohort study would report the duration of ETS as well as the (presumed) daily exposure and would use each subject's person-years of follow-up as the denominator in rate calculations and risk analysis. From Dr Hirayama's written descriptions of his study, such information is in his files or is available by linking a couple's initial questionnaire and death certificates.

SUMMARY & CONCLUSIONS

With the exception of Table 2 of (2), husband's age has been used to adjust for wife's mortality in a large and often quoted record linkage study in Japan 1966-1981. Our analysis shows that husband's age is *not* a surrogate for wife's age, in spite of its common use as such by Dr Hirayama. Since age at entry is confounded with cohort effects, it is also likely further that interactions occur between age and calendar period and between age and other covariates not represented in the model.

As a consequence of this finding, our conclusion is that the results of Hirayama's large study on ETS and lung cancer should *not* be pooled with other ETS/lung cancer studies to form a global estimate of relative risk. The relevance of this Japanese study's findings to public policy is questioned in the absence of more detailed information on exposure and follow-up, and more extensive analysis of the data at the level of the individual subject.

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